



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Indian Health Service
Rockville MD 20857

TO: Dockets Management Branch (HFA-305)
Food and Drug Administration
ATTENTION: Ms. Bonnie M. Lee

FROM: Acting Director
Office of Public Health

SUBJECT: Document No. OOD -0805
Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors:
Exception from Informed Consent Requirements for Emergency Research

The Indian Health Service (IHS) is providing comments on the above draft guidance document identified above. The IHS appreciates the care and effort that the Food and Drug Administration (FDA) has devoted to this topic. From prior comments that we have submitted, the exception from the usual requirements for informed consent for certain types of emergency research, excepting research from informed consent, is quite sensitive for many American Indian and Alaska Native (AI/AN) tribes, communities, and people. It is also sensitive for many other people of color who, like many AI/AN tribes and people, already have a high distrust of research.

The IHS submits the following suggestions for your consideration:

VI. Community consultation and public disclosure - General

This subsection helps clarify both "community consultation" and "public disclosure." Unfortunately many clinical investigators and even some IRBs think that both are one and the same. We suggest adding to the introduction (p.6) a brief paragraph that directly compares the two procedures.

The last paragraph of this subsection, p. 7, is somewhat confusing because it discusses two different "communities": the communities from which the participants will be drawn, and the "research community" and "scientific community" that will read the plans for the research and results of all research already done or being conducted. Because almost the entire draft Guidance uses the word "community" to mean only the former, we suggest two changes.

1. Separate the last two sentences of the paragraph, about "the research community" and "the scientific community," to a separate paragraph. The topic of those sentences is distinct from the topic of the first sentence.
2. Change "research community" and "scientific community" to "scientists and clinicians in the research topic" or similar term.

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VI. A. Community Consultation - When

We strongly agree with the draft that "encourages sponsors to work with clinical investigators and IRBs in developing model strategies" (p. 7). We suggest that the Guidance add "communities representatives" to the group developing model strategies. The IHS experience is helpful here. IHS (and the IHS IRBs) consult with the tribes to develop policy; we find that consultation has been invaluable, and results in a much better product than when only "outside experts" are involved. The entire Department of Health and Human Services is in the middle of an extensive tribal consultation process. We believe that communities can and should be involved at many steps of the process of emergency research, not only "reviewing the research itself" but also "developing model strategies for and approaches to community consultation."

VI. A. Community Consultation - Type and Frequency of Community Consultation

The draft Guidance appears to confuse the two different processes of "community consultation" and "public disclosure" in the second paragraph, p. 8: "A combination of these and other approaches may be necessary to ensure that communities involved in the research are adequately informed." We suggest the word "consulted" instead of "informed."

It is interesting that for all research involving AI/AN tribes, communities, and people, "community consultation" has been a requirement for almost 30 years. The IHS policy has prohibited involvement or support of any research that had not received formal approval by the tribal government[s] of the tribes involved. The IHS IRBs therefore require approval by the tribal government before their final IRB approval is given. We (and most researchers) have found that approval by the tribal government does take time, but is usually achievable when the researcher carefully and fully explains the research and modifies the research protocol to accommodate the concerns expressed. This almost 30-year-old requirement in Indian Country proves that community consultation can be done, and is valuable for the researcher, for the community, and ultimately for the research enterprise and the advancement of scientific knowledge.

The IHS recognizes that tribal sovereignty -- tribal governments have the legal power and jurisdiction to approve or disapprove research that is proposed to take place within the reservation -- is unique; other communities do not have similar legal jurisdiction. Thus, "community approval" is not a component of "community consultation" for purposes of this Guidance. The IHS suggests, however, that the Guidance insert a statement or paragraph in this subsection (or in the **Content** subsection) that for emergency research involving either an AI/AN tribe or Alaska Regional Corporation (ARC), community consultation must include formal approval by the tribal or ARC government.

In summary

The IHS finds this draft Guidance to be critically important to the field of emergency research.

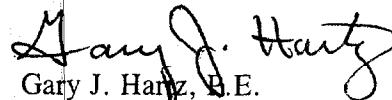
Waiving informed consent for participation in a clinical trial cannot be ethically justified by the scientific merit of the trial alone. The justification must also include processes that 'substitute' for individual informed consent. Individual informed consent is, among other things, a process by which not just scientists and IRBs (the members of which are predominately scientists and other professionals), but also the lay people who are the intended participants of the research, approve or disapprove the research. It is sobering to realize that every unethical research project conducted in the USA had been approved by several scientists and professionals.

The distrust toward research by some people, especially by AI/AN tribes and people and by other minority people, reflects their understanding that their interests may not always be protected by the good intentions of scientists and professionals. The processes of community consultation and public disclosure help reduce distrust arising from a waiver of consent, especially among AI/AN and other minority people, by two aspects:

- o community consultation and public disclosure ensure that the research is completely open and public, giving an opportunity to the general lay public to influence the research if it desires; and
- o community consultation gives an opportunity for the communities from whom individual people will be drawn to participate in the trial--without their consent--to influence the research easily and directly.

Not only do those two processes reduce distrust, they also provide the ethical justification for the absence of informed consent.

This draft Guidance is exceptionally good. The suggestions offered are intended to make it even better. Thank you for the opportunity to comment.



Gary J. Hartz, B.E.
Assistant Surgeon General

Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors

Exception from Informed Consent Requirements for Emergency Research

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Draft released for comment on March 30, 2000.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*. For questions regarding this draft document contact Bonnie M. Lee, (301) 827-0415, Internet Address blee@ora.fda.gov.

**U.S. Department of Health and Human Services
Food and Drug Administration
Office of Regulatory Affairs (ORA)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)**

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Exception from Informed Consent Requirements for Emergency Research (21 CFR 50.24)¹

I. INTRODUCTION

The information provided in this guidance is intended to assist product sponsors, clinical investigators, and Institutional Review Boards (IRBs) in (1) the development and implementation of research in emergency settings when an exception from the informed consent requirements is requested under 21 CFR 50.24; and (2) understanding their responsibilities for communicating with, and submitting information to, FDA.

The regulations (Title 21, Code of Federal Regulations [21 CFR] Section 50.24, and conforming amendments contained in 21 CFR Parts 56, 312, 314, 601, 812, and 814) provide an exception to the requirement to obtain informed consent from each subject, or the subject's legally authorized representative, prior to enrollment in a clinical investigation. The exception applies to emergency research (1) for which an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) is in effect, (2) involving human subjects who cannot give informed consent because of their emerging, life-threatening medical condition (for which available treatments are unproven or unsatisfactory), and (3) where the intervention must be administered before informed consent from the subjects' legally authorized representative is feasible. Studies involving an exception from informed consent requirements may proceed only after a sponsor has received prior written permission from FDA, and the IRB has found and documented that specific conditions have been met.

The emergency research permitted under 21 CFR 50.24 involves a particularly vulnerable population: persons with life-threatening conditions who can neither give informed consent nor actively refuse enrollment. This lack of autonomy creates a special need for FDA, sponsors, IRBs, and clinical investigators to work closely together to ensure that the interests of this vulnerable population of subjects are protected to the maximum extent possible. The regulations for emergency research therefore contain specific human subject protection requirements in addition to the requirements pertaining to all IND and IDE clinical studies. These include specific requirements that representatives of the community(ies) in which the research will take place and from which the subjects will be drawn be consulted about the study, that information about a study be publicly disclosed before the study may proceed, and that the sponsor submit a

¹This guidance has been prepared by a Working Group composed of representatives from the Food and Drug Administration's Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Center for Food Safety and Applied Nutrition, the Center for Veterinary Medicine, the Office of Regulatory Affairs, the Office of the Executive Secretariat, and the Office of the Chief Counsel. This guidance represents the Agency's current thinking on applications that contain a request for an exception from informed consent requirements for emergency research. It sets forth guidelines for IRBs, sponsors, and investigators. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An electronic version of this guidance is also available via Internet using the World Wide Web (WWW). To access the document on the WWW, connect to the FDA Home Page at www.fda.gov/oc/oha/toc.html.

separate IND or IDE for the study.

The emergency research regulations became effective November 1, 1996. Since that date, FDA has reviewed the efforts of sponsors, IRBs, and clinical investigators to interpret and comply with these regulations and has determined that guidance is needed in several areas, particularly in the development and conduct of community consultation and public disclosure activities and the establishment of informed consent procedures to be used when feasible. This document also provides guidance related to other aspects of the emergency research regulations, including the need for the concurrence of a licensed physician, use of data monitoring committees, use of independent IRBs, and the documentation of efforts to contact a subject's legally authorized representative or family member regarding the subject's participation in the study.

Because this type of research involves incapacitated patients who will not be able to give their informed consent as a result of their medical condition, a unique IND or IDE is required. If necessary, FDA may place a proposed or ongoing emergency research investigation (or study site) on clinical hold (1) if any of the conditions in 21 CFR 312.42(b)(1) or (b)(2) apply; or (2) if the pertinent criteria in 21 CFR 50.24 for such an investigation to begin or continue are not met. FDA may disapprove or withdraw approval of an IDE under 21 CFR 812.30 for failure to comply with "any other applicable regulation or statute, or any condition of approval imposed by an IRB or FDA."

II. STUDY DESIGN

Prospect of Direct Benefit

Participation in emergency research studies must hold out the prospect of *direct benefit* to the individual subject [21 CFR 50.24(a)(3)]. Sponsors should provide assurances that the risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity. In addition, sponsors should provide assurance that the study hold out the prospect of direct benefit to the individual subject.

Subject Exclusion

Study protocols may describe situations in which emergency care personnel could reasonably infer that some incapacitated individuals would not agree to participate in a research study, even if the individuals meet the inclusion criteria. For example, members of some religious groups object to blood transfusions and other medical interventions. Clinical investigators should examine easily accessible sources of information, such as an individual's driver's license or medical jewelry, for evidence related to that individual's willingness to participate in research.

Designs

The regulations do not limit study designs for conducting emergency research;

the study design should be adequate to the task of evaluating whether the drug or device has the hypothesized effect.

Placebo-controlled trials may be conducted under this emergency research provision, when appropriate [21 CFR 50.24(a)(1)]. In virtually all cases, when a placebo is used, standard care, if any, would be given to all subjects, with subjects randomized to receive, in addition, either the test treatment or a placebo.

An exception would be the situation in which the study objective is to determine whether standard treatment is in fact useful. In that case, there would be a group that does not receive the standard treatment. Sponsors designing placebo-controlled trials that include subjects to whom neither standard treatment nor the test article is given should provide a sound rationale for this type of study design.

III. THERAPEUTIC WINDOW

Definition The therapeutic window is the time period, based on available scientific evidence, during which administration of the test article might reasonably produce a demonstrable clinical effect.

Therapeutic Window Rationale The therapeutic window cannot be known until the relation of time of treatment to treatment outcome is formally studied. Nevertheless, the sponsor must use available data (e.g., pathophysiologic data, animal data) to identify the therapeutic window during which administration of the test article to study subjects should be initiated [21 CFR 50.24(a)(5)]. The therapeutic window should be specified in the study protocol, as well as the amount of time to be devoted to seeking informed consent, as explained below.

Contact of Family Members In identifying the therapeutic window, sponsors should recognize that attempts to contact a legally authorized representative or a family member (if no legally authorized representative is available) need not exhaust the entire therapeutic window before the test article may be administered. In some circumstances, e.g., cardiac arrest, the therapeutic window may be very short. Ordinarily, it may be expected that the potential benefit of the test article would decrease as the time for administering the test article increases. Thus, the effect of delaying administration of the test article should be taken into account when determining the portion of the therapeutic window to be devoted to seeking informed consent from a legally authorized representative or providing the opportunity for a family member to object to the subject's participation.

The IRB should review the proposed plan and procedures for attempting to contact the legally authorized representative or family member and determine whether the specified period of time for making these attempts before the test

article may be administered is appropriate.

IV. IRB REVIEW

FDA anticipates that emergency research usually will be performed at an institution with an IRB that has the responsibility and authority to review all studies performed at that institution. Independent IRBs, however, may review emergency research studies involving an exception to the informed consent requirements, provided that they comply with all the regulatory requirements, including the community consultation and public disclosure provisions. The institutional responsibility for IRB review should not be delegated to another IRB unless the institution and the IRB for the institution agree to the delegation and the agreement is documented in writing [21 CFR 56.114].

V. LICENSED PHYSICIAN CONCURRENCE REQUIRED FOR IRB APPROVAL OF THE RESEARCH

The IRB must have the concurrence of a licensed physician, both initially and at the time of continuing review, that the criteria of 21 CFR 50.24 are met. The licensed physician must be "a member of or consultant to the IRB and . . . not otherwise participating in the clinical investigation" [21 CFR 50.24(a)]. A licensed physician consultant would be necessary in cases where the licensed physician member(s) cannot participate in the deliberation and voting due to conflict(s) of interest. Because the documented concurrence of the licensed physician member or licensed physician consultant is required for the IRB to allow these studies to proceed, IRBs should ensure that meeting minutes specifically record the licensed physician member's affirmative vote or the licensed physician consultant's concurrence.

VI. COMMUNITY CONSULTATION AND PUBLIC DISCLOSURE - General

Under 21 CFR 50.24, community consultation and public disclosure must be provided for each emergency research protocol for which an exception from informed consent is requested.

Community consultation refers to ensuring that the community(ies) is (are) involved in the IRB's decision-making process. As such, the IRB needs to provide an opportunity for the community(ies) to discuss the proposed clinical investigation and its risks and potential benefits, and to provide feedback to the IRB. The IRB should consider this community discussion when reviewing the protocol.

Public disclosure refers to informing the community(ies), the public, and researchers about the study (1) prior to its commencement and (2) following its completion.

Prior to commencement of the study, there must be public disclosure of sufficient information

to describe the nature and purpose of the study, the fact that informed consent will not be obtained for most study subjects, and the study's risks and potential benefits [21 CFR 50.24(a)(7)(ii)]. For example, relevant information could be obtained from the investigator's brochure and study protocol. Disclosure of this information should inform individuals within the community(ies) about the clinical investigation.

Following completion of the study, information about the study results should be disclosed to the community(ies) from which the subjects were drawn and in which the study was conducted [21 CFR 50.24(a)(7)(iii)]. In addition, the research community should have access to comprehensive summary data from the completed trial in order to permit researchers to assess the results of the clinical investigation. Making the research results broadly known to the scientific community, through scientific publication or meetings, may reduce or eliminate the possibility that research (which has been conducted or verified by others) is not unnecessarily duplicated.

A. COMMUNITY CONSULTATION

Before a clinical study may be initiated, the IRB must find and document that consultation has occurred with representatives of the community(ies) in which the research will take place and from which research subjects may be drawn [21 CFR 50.24(a)(7)(i); 21 CFR 56.115(a)].

Definitions **Community consultation.** Community consultation means providing the opportunity for discussions with, and soliciting opinions from the community(ies) in which the study will take place and from which the study subjects will be drawn. These communities may not always be the same; when they are not the same, both communities should be consulted.

The **community in which the research will take place** is the geographic area, e.g., city or region, where the hospital or clinical investigator study site is located.

The **community from which subjects will be drawn** may be characterized by analyzing the demographics of previous hospital patients with the emergent condition under study. For example, the IRB or clinical investigator might review the hospital records of the last 50-100 patients admitted to the emergency room for the condition under study and tabulate characteristics (gender, age, ethnicity, geographic locale, etc.)

When Consultation must occur prior to initiation of the study [21 CFR 50.24(a)(7)(i)]. FDA encourages sponsors to work with IRBs and clinical investigators in developing model strategies and plans for consultation with the community(ies).

Costs Although FDA does not dictate who should bear the costs associated with

consultation with the community(ies), the agency anticipates that the sponsor would normally bear the costs because consultation is a requirement for conducting the research.

**Type &
Frequency
of
Community
Consultation**

It is the shared obligation of the clinical investigator, IRB, and sponsor to make the effort to reach the community(ies). IRBs and clinical investigators should provide opportunities for representatives of the community(ies) involved in the research to discuss the proposed clinical investigation, for example, in face-to-face meetings, with the IRB and investigators. The meetings should include discussions of (1) the fact that informed consent will not be obtained for most study subjects and (2) the risks and potential benefits of the research for study subjects. In conducting community consultation activities, IRBs and clinical investigators should ensure that representatives from the community(ies) involved in the research are informed of, and participate in, the consultation process.

IRBs and clinical investigators should choose the most appropriate way to provide community consultation. Standing meetings, such as local civic public forums, may be better attended because such meetings are already on community members' calendars. Organizing special meetings specifically to discuss the research may be valuable in that such meetings may draw participation from individuals with strong interest in the research. The agency recognizes that other methods to consult with the community(ies) may be appropriate in some instances, for example, the use of local radio and/or television talk shows that allow viewers to "call-in" to express their views and concerns. A combination of these and other approaches may be necessary to ensure that communities involved in the research are adequately informed. Consultation activities should be widely advertised so that representatives of as many different groups within the community(ies) as possible are included.

In addition, the IRB might invite community representatives to participate in convened or special meetings of the IRB at which the emergency research will be discussed. Alternatively, the IRB could use community members as consultants to the IRB or establish a separate IRB subpanel of members of the community(ies) from which the subjects will be drawn. The clinical investigator and one or more IRB members should attend each community consultation meeting to answer questions and gain firsthand knowledge about the communities' reactions to and concerns about the research.

The number of members of the community(ies) that should be consulted and the number of meetings that should be held for adequate consultation will vary depending upon the size of the community(ies), the homogeneity of the subject population, the languages spoken within those communities, the targeted research

population, etc.

IRBs should assess the success and determine the adequacy of consultation efforts, i.e., whether meaningful feedback was secured from the community(ies).

For example, low attendance at meetings should not be construed as meaning that there is no interest in or no objection to the research by the community(ies).

Limited or no input from the community(ies) may mean that additional efforts need to be made to reach the community(ies).

Content

Consultation provides the initial opportunity for the IRB and clinical investigator(s) to inform community representatives (1) that informed consent will not be obtained for most research subjects; (2) about the risks and potential benefits of the research; and (3) about an individual's right to refuse to participate in research and ways in which individuals wishing to be excluded may indicate this preference. The community representatives are expected to provide input to the IRB on community support for, or concerns about, the research activity. Thus, the consultation should involve an exchange of information about the study and community attitudes with respect to the research.

As required by 21 CFR 56.107(a), the IRB is responsible for listening to and considering the community's opinions and concerns when deciding whether the investigation should be modified, approved, or disapproved. For example, in response to the community's concerns, the IRB may agree that it is appropriate to limit the universe of people from which potential subjects may be drawn by excluding particular populations who voice opposition to participation in the investigation, provided that members of those groups can be easily identified. In some cases, the IRB may determine that additional community consultation activities are necessary to help the IRB members better understand concerns and objections to the study raised by specific groups within the community. In other cases, if the community raises objections and concerns, an IRB may determine that the study should not be performed in its community.

IRBs must include in their minutes a written summary of the discussion of controversial issues and their resolution. This would include controversial issues raised during community consultation activities, particularly discussions of community opposition to, or concern about, the emergency research study, and how the IRB addressed and/or resolved such concerns about the study [21 CFR 56.115(a)(1) and (2)].

Advice for Public Disclosure Consultation with community representatives may provide a good opportunity for IRBs and clinical investigators to obtain important advice on how to provide efficient and effective disclosure to the broader community.

B. PUBLIC DISCLOSURE

Public disclosure is required (1) before the emergency research may begin and (2) after the research has been completed. The IRB must find and document that public disclosure has occurred [21 CFR 50.24(a)(7)(ii) and (iii); 21 CFR 56.115(a)].

Although FDA does not dictate who should bear the costs associated with public disclosure activities, the agency anticipates that the sponsor would normally bear the costs because public disclosure is a requirement for conducting the research.

Definition Public disclosure means dissemination of information about the emergency research sufficient to allow a reasonable assumption that the communities are aware that the study will be conducted, and later, that the communities and scientific researchers are aware of the study's results.

1. BEFORE THE STUDY BEGINS

Who The IRB is responsible for finding and documenting that information about the emergency research has been publicly disclosed.

Clinical investigators and IRBs are responsible for making the arrangements for public disclosure of plans for the investigation and the investigation's risks and potential benefits. FDA encourages sponsors to work with clinical investigators and IRBs in developing model strategies and information for public disclosure as early as possible.

When Public disclosure must occur prior to initiation of the clinical investigation [21 CFR 50.24(a)(7)(ii)]. In addition, the IRB may determine that it is appropriate to require additional disclosure at periodic intervals of time.

Content In order for the community to understand the anticipated risks and potential benefits of the study, the clinical investigator and IRB must disclose the study plans to the public [21 CFR 50.24(a)(7)(ii)]. This disclosure could include information that is found in the informed consent document, the investigators' brochure, and the research protocol. The disclosure should clearly state that informed consent will not be obtained for most research subjects. It should also include information about the test article's use, a balanced description of the risks

and potential benefits, a synopsis of the research protocol and study design, how potential study subjects will be identified, and the sites or institutions that will be participating in the research. Disclosure should explain what attempts will be made to contact a legally authorized representative, or, if no legally authorized representative is available, a family member about the subject's participation in the study, both before and after the test article is administered. In some studies, the therapeutic window will be very short. Disclosure should also explain how individuals who do not want to participate in the research can communicate their desire not to participate (e.g., by use of medic alert bracelets, statements on driver's license, etc.)

How

FDA anticipates that multiple forums and media resources will be needed to widely disseminate information about the study. For example, disclosure activities could include advertisements and articles in English language, and if appropriate, foreign language, newspapers; information on an Internet web site; information at meetings of community, local government, civic, or patient advocacy groups, such as Rotary, League of Women Voters, religious organizations, senior citizens groups; and public service announcements and interviews or discussions on "talk" radio or television programs; press conferences and briefings.

Another avenue for public disclosure to the community might be provided by hospitals' and institutions' existing community outreach programs.

Public disclosure activities should provide sufficient information about the emergency research so that community members can easily learn about the research planned for their community(ies). For example, the following activities alone or in combination with each other would not constitute sufficient public disclosure under this rule: a legal notice; sending a letter to physician specialists about the study; or informing hospital staff about the study.

**Publicly
Disclosed
Information**

The IRB must provide the sponsor with a copy of the information that was publicly disclosed (e.g., copies of newspaper advertisements, tapes or transcripts of radio and television shows, minutes of community meetings) so that the sponsor is aware that such disclosure has occurred and can provide copies of the disclosed information to FDA [21 CFR 56.109(g), 312.54(a) and 812.47(a)].

**Access
to Public
Disclosure
Information**

Upon receiving from the IRB copies of the information that has been publicly disclosed, the sponsor must submit the information to FDA, to the IND/IDE and to Dockets Management at the following address [21 CFR 312.54(a) and 21 CFR 812.47(a)]:

Docket Number 95S-0158 (IND#/IDE#)
Dockets Management Branch

Food and Drug Administration
Room 1061, Mail Stop HFA-305
5630 Fishers Lane
Rockville, MD 20852

Telephone: 301/827-6860
Fax: 301/827-6870

Members of the public wishing to examine public disclosure information submitted to the docket may visit the FDA's Dockets Management Branch or request copies by sending a Freedom of Information Act request to FDA at the address shown below [21 CFR 312.130(d) and 812.38]:

Freedom of Information Office (HFI-35)
Food and Drug Administration
5600 Fishers Lane
Room 12A-16
Rockville, MD 20857

Telephone: 301/827-6500

2. AFTER THE STUDY IS COMPLETED

Following completion or termination of a clinical investigation, there must be public disclosure of sufficient information (including the demographic characteristics--age, sex, race--of the research population) to apprise the lay and research communities of the results of the study [21 CFR 50.24(a)(7)(iii)].

Who

The sponsor is responsible for analyzing the results of the overall investigation, including the demographic characteristics of the research population, and for ensuring that these results are published (or reported) in the lay press.

The IRB(s) must find and document that the information to be disclosed to the community(ies) and researchers is sufficient to apprise them of the study results, including the demographic characteristics of the research population [21 CFR 50.24(a)(7)(iii)]. FDA anticipates that the sponsor and clinical investigator(s) will review the information with the IRB(s) prior to disclosure.

When

Disclosure of the study results to the community(ies) should occur in a timely fashion following completion of the investigation. For a multi-site investigation, this would ordinarily require waiting until the data from all sites have been analyzed by the sponsor.

How

Comprehensive summary data from the completed trial should be prepared and

made available to the research community (e.g., through publication in scientific journals, discussion at symposia) in order to permit other researchers to assess the results of the clinical investigation.

The IRB is responsible for assuring that appropriate mechanisms are used (e.g., news articles, television or radio programs, community meetings) for providing information about the results of the research to the community(ies) in which the clinical investigation was conducted and from which research subjects were drawn. IRBs should ensure that study information is stated in language understandable to these communities.

Regulations regarding the promotion of investigational drugs and devices also apply to disclosure of study results; that is, a sponsor or investigator shall not represent in a promotional context that an investigational new drug, biologic, or device is safe or effective for the purposes for which it is under investigation, or otherwise promote the drug or device [21 CFR 312.7 and 812.7].

See also "Publicly Disclosed Information" in section VI.B.1, above, for details on submission of public disclosure information to FDA.

VII. CONTACT OF LEGALLY AUTHORIZED REPRESENTATIVES OR FAMILY MEMBERS

A. PRIOR TO ADMINISTRATION OF THE TEST ARTICLE

Commitment For each subject unable to provide informed consent, the clinical investigator participating in emergency research must commit to attempting to seek written informed consent, if feasible, from a legally authorized representative or, if no legally authorized representative is available, to provide an opportunity for a family member to object to the participation of an individual, before administering the test article without informed consent [21 CFR 50.24(a)(7)(v)].

Procedures IRBs must find and document that procedures are in place for contacting and providing information to a subject's legally authorized representative or family member [21 CFR 50.24(b)]. FDA anticipates that procedures and information will likely parallel those approved by the IRB for use in obtaining informed consent from subjects or their legally authorized representatives. Each study site should therefore have procedures in place for each emergency research protocol that will be used (1) in attempting to obtain informed consent from a legally authorized representative, and (2) if no legally authorized representative is available, in attempting to contact a family member and provide an opportunity for the family member to object, prior to enrolling a subject in the study and administering the test article.

- Informed Consent Document** An IRB-approved informed consent document, consistent with 21 CFR 50.25, must be available. Informed consent must be obtained, when feasible, from the subject or the subject's legally authorized representative [21 CFR 50.24(a)(6)].
- Opportunity To Object** Family members are not required to sign a document to object to an individual's participation in a study. Objections should be documented, for example, by placing appropriate entries in the individual's medical charts. When a legally authorized representative is unavailable, if a family member objects to an individual's participation in the study, the individual should not be entered into the study. If family members were to disagree, the researcher and family members would need to work out the disagreement.
- Summary of Contact Efforts** The clinical investigator is required to summarize the efforts made to contact a legally authorized representative or, if no legally authorized representative is available, a family member for each subject within the therapeutic window. This information must be provided to the IRB at the time of continuing review of the study [21 CFR 50.24(a)(5) and (a)(7)(v)].

B. AFTER ADMINISTRATION OF THE TEST ARTICLE

- When** IRBs must ensure there are procedures in place to provide information about the emergency research study, at the earliest feasible opportunity, to (1) the subject if the subject recovers from the life-threatening event, (2) the subject's legally authorized representative (if the subject remains incapacitated), or (3) the subject's family member (if no legally authorized representative is available), including notice that the subject may withdraw or discontinue participation in the study without penalty or loss of benefits to which the subject is otherwise entitled [21 CFR 50.24(b)].
- IRBs must also ensure that in the event of the subject's death, there are procedures in place to provide information about the study to the legally authorized representative or family member (if no legally authorized representative is available), if feasible [21 CFR 50.24(b)]. The regulations do not contain a time limit for providing this information, in order to allow consideration of the emotional condition of the family members who have just learned of the death. A hospital chaplain or social worker may be helpful in determining the appropriate time to discuss the clinical investigation.
- Records** The clinical investigator should include in the subjects' case histories attempts to inform each subject, a legally authorized representative or, if no legally authorized representative is available, a family member, of the subject's inclusion in the clinical investigation [21 CFR 50.24(a)(7)(v)].

Agreement for Continued Participation in Study The IRB should determine whether it is desirable, given the nature of a clinical investigation, to have an actual document that could be signed by the subject or the subject's legally authorized representative for continued participation in an investigation. Such a document, if signed after entry into an investigation, would not constitute informed consent for what had already occurred, but would serve to document that the subject or the subject's legally authorized representative agreed to continue the subject's participation in the study.

VIII. DATA MONITORING COMMITTEE (DMC)

Before a study may be initiated, the IRB must find and document that the sponsor has established an independent DMC to serve as an advisory body to the sponsor [21 CFR 50.24(a)(7)(iv)].

Definition A data monitoring committee, sometimes called a data and safety monitoring board, is a group of experts established by the sponsor to assess at intervals the progress of a clinical trial (the safety data and the critical efficacy endpoints), and to recommend to the sponsor whether to continue, modify, or stop a trial. DMCs for trials implemented under 21 CFR 50.24 must be "independent", by which the agency means that the committee should be composed solely of individuals who have no financial interest in the outcome of the study and who have not been involved in the design or conduct of the study [21 CFR 50.24(a)(7)(iv)].

Purpose The DMC helps ensure subject safety by reviewing ongoing results on a periodic basis and considering whether an investigation ought to be modified to minimize any identified risks or halted. Factors to consider in this decision include whether (1) the potential benefits of the investigational intervention have been established or (2) the risks are greater than anticipated.

The DMC is responsible for informing and making recommendations to the sponsor about safety or efficacy concerns related to continuing the investigation.

Membership The DMC should be composed of individuals not otherwise connected with the particular clinical investigation or the sponsor. A DMC under this rule typically would include one or more clinicians specializing in the relevant medical field(s), biostatisticians, and bioethicists.

Operation The DMC reviews study data and adverse event reports on a schedule generally defined by the sponsor, which may include review of study data on an ongoing basis (real time) if necessary for adequate safety monitoring in specific situations.

It is essential that the DMC have access to all the information it needs to effectively evaluate the progress of the study. Thus, the DMC may need access to data unblinded by treatment arms in order to ensure reliable and complete assessment of the safety and efficacy data.

The sponsor is responsible for determining the scope of the DMC's responsibilities. Operations of the DMC should include:

- (1) the manner in which, and the frequency with which, study data and information about adverse events are forwarded to and reviewed by the DMC, e.g., after 10%, 25%, 50%, 75%, or 100% enrollment;
- (2) criteria for assessing data, and pre-established "stopping" criteria;
- (3) qualifications of DMC members;
- (4) assurance that members of the DMC have no financial interest in the outcome of the study and have not been involved in the design or conduct of the study; and
- (5) preparation and maintenance of written records for all meetings.

**May an
IRB Serve
as a DMC?**

Because most IRBs are not constituted to meet the special membership requirements of a DMC, and the duties and scope of activities of an IRB and a DMC are quite different, entities performing each of these separate functions should be established. Any committee serving as a DMC should ensure that its membership is appropriate to the study and that it operates as a separate, independent entity.

IX. FOR FURTHER INFORMATION

A. CONTACTS

Sponsors and IRBs with questions regarding applications pertaining to an exception from informed consent requirements for emergency research under 21 CFR 50.24 may contact the appropriate office(s) identified below:

CBER: (Center for Biologics Evaluation & Research)

Office of Compliance and Biologics Quality
Bioresearch Monitoring Team (HFM-650)
1401 Rockville Pike
Rockville, MD 20852-1448

301/827-6221; fax: 301/827-6748

CDER: (Center for Drug Evaluation & Research)

Regarding informed consent procedures and documents:

Division of Scientific Investigations

Good Clinical Practice Branch I and II (HFD-344)

7520 Standish Place

Rockville, MD 20855

301/594-1026; fax: 301/594-1204

Regarding specific applications/INDs:

Office of Drug Evaluation - I (HFD-101)

1451 Rockville Pike, Room 6015

Rockville, MD 20852-1420

301/594-6758; fax: 301/594-5298

CDRH: (Center for Devices and Radiological Health)

For questions about 21 CFR 50.24 implementation and specific applications:

Office of Device Evaluation (IDE Staff)

9200 Corporate Boulevard

Rockville, MD 20850

301/594-1190; fax: 301/594-2977

ORA: (Office of Regulatory Affairs)

Office of Enforcement

Bioresearch Monitoring Program Coordinator (HFC-230)

5600 Fishers Lane

Rockville, MD 20857

301/827-0415 or 301/827-0425; fax: 301/827-0482

FDA will place the publicly disclosed information related to emergency research studies under 21 CFR 50.24 submitted to the agency by the sponsor, in Docket Number 95-S0158, identified by the IND/IDE number. This information can be viewed by visiting the Dockets Management Branch (HFA-305), FDA, 5630 Fishers Lane, Room 10-61, Rockville, MD 20852. These documents are also available under the provisions of the Freedom of Information Act (FOIA) [21CFR 312.54(a), 312.130(d) and 812.38]

Members of the public wishing to examine the public disclosure information submitted to the docket may visit the docket or request copies by sending a Freedom of Information Act request to FDA [21 CFR 312.130(d) and 812.38].

COMMENTS ON THIS GUIDANCE SHOULD BE SUBMITTED TO:

Dockets Management Branch (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket # _____.

B. REFERENCES

- 1) Protection of Human Subjects; Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research; Final Rules, Federal Register (FR), 61 FR 51498, October 2, 1996.
- 2) Protection of Human Subjects; Informed Consent; Proposed Rule, 60 FR 49086, September 21, 1995.
- 3) Hearing before the Subcommittee on Regulation, Business Opportunities, and Technology, Committee on Small Business, U.S. House of Representatives, May 23, 1994.
- 4) Coalition Conference of Acute Resuscitation and Critical Care Researchers, Consensus (October 25, 1994)
- 5) FDA-NIH Public Forum on Informed Consent in Clinical Research conducted in Emergency Circumstances, transcript, January 9-10, 1995.
- 6) Implementation of Emergency Research Informed Consent Waiver Rule; Public Meeting, September 29-30, 1997, Bethesda, MD.

X. APPENDICES

APPENDIX A

RESEARCH THAT MAY NOT BE INITIATED UNDER 21 CFR 50.24

A clinical investigation that involves a request for an exception from informed consent requirements for emergency research under 21 CFR 50.24 may not be initiated:

- (1) If FDA does not allow the IND to proceed, or approve the IDE, or the IRB does not approve the research protocol covered by that IND or IDE.
- (2) If state or local law(s) prohibits entry of subjects into research without their express consent. 21 CFR 50.24 does not preempt state or local laws. Those conducting emergency research need to be familiar with the laws of the specific states in which the research will be conducted.
- (3) If scientifically sound research can be practicably carried out using subjects who can be identified prospectively or give informed consent directly, or for whom legally authorized representative(s) provide informed consent. For example, advance informed consent could possibly be obtained from a subject who suffers from a particular disease or condition that places him/her at an extremely high risk for a serious event, e.g., surgical patients at high risk for intra-operative stroke, cardiac patients at high risk for cardiac arrest, already hospitalized and acutely ill patients, etc.

[Note: Judgment must be exercised, however, in deciding whether prospective consent is realistic, and thus, whether a study using this approach is practicable. For example, it may not be practicable to obtain advance consent from a large number of patients at the time they enter a hospital so they could participate in a post-arrest study that would involve only a small fraction of those patients.]

- (4) If an unconscious or otherwise incapacitated individual does not need immediate intervention to prevent death and there is sufficient time to locate and obtain informed consent from a legally authorized representative prior to administration of the test article. An exception to the informed consent requirements under 21 CFR 50.24 is not intended to apply to persons who are not in an emergent situation (e.g., have been in a long-term coma) nor to subjects for whom prospective informed consent is feasible.

If a physician wishes to use an investigational test article in an attempt to save the life of a patient, the exception from informed consent procedures provided under 21 CFR 50.23(a) and (b), and 812.35(a)(2) should be followed.

APPENDIX B DEFINITIONS

Clinical investigation. [Note: The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this guidance.]

The term means:

For drugs/biologics: Any experiment in which a drug/biologic is administered or dispensed to, or used involving, one or more human subjects [21 CFR 312.3(b)].

For devices: Any investigation or research involving one or more subjects to determine the safety or effectiveness of a device [21 CFR 812.3(h)].

Clinical Investigator. An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of that team [21 CFR 312.3(b), 812.3(i)].

Community. A community means a group or groups of people who live and work in a particular region and who may be linked by common interests; an interacting population of different kinds of individuals constituting a society or association; or, simply an aggregation of mutually related individuals in a given location [Webster's Third New International Dictionary, c. 1971].

Community consultation. Community consultation means providing the opportunity for discussions with, and soliciting opinions from the community(ies) in which the study will take place and from which the study subjects will be drawn. These communities may not always be the same; when they are not the same, both communities should be consulted.

Data Monitoring Committee (DMC). A data monitoring committee, sometimes called a data and safety monitoring board, is a group of experts established by the sponsor to assess at intervals the progress of a clinical trial (the safety data and the critical efficacy endpoints), and to recommend to the sponsor whether to continue, modify, or stop a trial.

Disclosure. See public disclosure.

Emergency Research. A planned clinical investigation that is subject to FDA authorization in advance and involves subject(s) who are experiencing immediately life-threatening conditions for which available treatments are unproven or unsatisfactory.

Family member. Any one of the following legally competent persons: spouse, parents, children (including adopted children), brothers, sisters, and spouses of brothers and sisters, and

any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship [21 CFR 50.3 (n)]. Definition of "legally competent" may vary by state but in general includes an age of majority and an assessment of mental capacity.

Institutional Review Board (IRB). Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such a review is to ensure the protection of the rights and welfare of the human subjects [21 CFR 56.102(g)].

Investigator. See clinical investigator.

Legally authorized representative. An individual or judicial or other body authorized under applicable law to give informed consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research [21 CFR 50.3(m)]. IRBs and clinical investigators should familiarize themselves with applicable local statutes and regulations pertaining to the definition of a legally authorized representative.

Life-threatening. Diseases or conditions where the likelihood of death is high unless the course of the disease or condition is interrupted. 21 CFR 50.24 applies only to life-threatening EMERGENCY situations.

Public disclosure. Public disclosure means dissemination of information about the emergency research sufficient to allow a reasonable assumption that the communities are aware that the study will be conducted, and later, that the communities and scientific researchers are aware of the study's results.

Sponsor. A person who takes responsibility for and initiates a clinical investigation [21 CFR 312.3(b), 812.3(n)]. A sponsor may be an individual, a company, a governmental agency, an academic institution, a private organization, etc.

Sponsor-Investigator. An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational test article is administered or dispensed [21 CFR 312.3(b), 812.3(o)]. A sponsor-investigator assumes the responsibilities of both sponsors and clinical investigators.

Therapeutic window. The therapeutic window is the time period, based on available scientific evidence, during which administration of the test article might reasonably produce a demonstrable clinical effect.